FASS

Exelon®

Novartis

Kapsel, hård 4,5 mg

(Tillhandahålls för närvarande ej) (Benvit till svagt gulfärgat pulver i kapsel med rött lock och röd underdel med vit inskrift "EXELON 4.5 mg" på underdelen.)

Kolinesterashämmare

Aktiv substans:

Rivastigmin

ATC-kod:

N06DA03

Läkemedel från Novartis omfattas av Läkemedelsförsäkringen. Läkemedlet distribueras också av företag som inte omfattas av Läkemedelsförsäkringen, se Förpackningar.

Miljöpåverkan

Rivastigmin

Miljörisk: Användning av rivastigmin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Rivastigmin är potentiellt persistent.
Bioackumulering: Rivastigmin har låg potential att bioackumuleras.

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.5*10^{-6} * A * (100 – R) = 1.5*10^{-6} * 29.3529$ kg * 100

PEC = 0.0044 µg/L

Where:

A = 29.3529 (Sum of 24.6529 kg rivastigmine and 4.7 kg normalized to the base from 7.5168 kg rivastigmine hydrogentartrate) (total sold amount API in Sweden year 2015, data from IMS Health).

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available.

P = number of inhabitants in Sweden = $9 *10^{6}$

V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (ECHA 2008)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default) (ECHA 2008)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (Selenastrum capricornutum) (OECD201) (ABC Laboratories Final Report 43080)*:*

EC50 72 h (growth rate) > 83.0 mg/L

NOEC = 10 mg/L (value of the tartrate salt)

Crustacean (Daphnia magna):
Acute toxicity
EC50 48 h (immobilisation) = 1.4 mg/L (EPA-660/3-75-009) (ABC Laboratories Final Report 43078)
Chronic toxicity
NOEC 21 days (parental mortality and number of offspring) = 0.5 mg/L (value of the base) (OECD 211) (RCC study no.: B40476)

Fish:
Acute toxicity (*Lepomis macrochirus,* bluegill sunfish)
LC50 96 h (mortality) = 31.8 mg/L (value of the tartrate salt) (EPA-660/3-75-009) (ABC Laboratories, Final Report 43079)
Chronic toxicity (*Danio rerio*, zebra fish)
NOEC 35 days (survival of larvae and juvenile fish) = 1.3 mg/L (value of the base) (OECD 210) (RCC study no.: B40498)

Other ecotoxicity data:

Bacterial respiration inhibition
EC_{50} 3h > 1000.0 mg/L (activated sludge respiration inhibition) (value of the base) (OECD209) (RCC Study No.: B40465)

Sediment-dwelling organisms (*Chironomus riparius*, non-biting midge)
NOEC 28 days (emergence rate and development rate) = 0.24 mg/L (value of the base) (OECD 219) (Harlan Laboratories Study No.: C06282)

PNEC derivation:

PNEC = 50.0 µg/L
PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for *Daphnia magna* reproduction has been used to derive the PNEC for rivastigmine.

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.0044 µg/L / 50.0 µg/L = 0.000088, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase "Use of rivastigmine has been considered to result in insignificant environmental risk."

Degradation

Biotic degradation

Ready degradability:
5.0 % degradation in 28 days, not readily biodegradable (FDA TAD3.11). (ABC Laboratories Final Report 42970)
Simulation studies:
DT50 (total system) = 119 - 266 days
DT90 (total system) = 457 - 882 days (OECD 308). (RCC Study No.: B40454)
Sediments were exhaustively extracted with acetonitrile/water (4:1; v/v). Soxhlet extraction using the same solvent mixture was additionally performed on the sediments from day 1 onwards. The amount of non-extractable radioactivity was significant for both test systems. Bound radioactivity in the sediment reached maximum mean levels of 26% and 32% on day 100.

Justification of chosen degradation phrase:

Based on the fact that rivastigmine is not readily biodegradable and according to the pass criteria for OECD308 studies, rivastigmine can be classified as ‘Rivastigmine is potentially persistent.’
(DT50 for total system > 120 days)

Bioaccumulation

Partitioning coefficient:
Log K_{ow} = 2.16 at pH 10
Log K_{ow} < 1 at pH 7 (FDA TAD 3.02 'shake-flask method, value of the tartrate salt) (ABC Laboratories Final Report 42967)
Justification of chosen bioaccumulation phrase:
Since log K_{ow} < 4 at pH 7, rivastigmine has low potential for bioaccumulation.

Excretion (metabolism)

Rivastigmine is rapidly and extensively metabolised, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase. Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90 %) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. (Novartis Core Data Sheet Exelon® (rivastigmine))

PBT/vPvB assessment

Based on screening criteria, rivastigmine has low potential for bioaccumulation and can therefore not be considered a potential PBT or vPvB substance.

References

- ECHA 2008, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/informa
- ABC Laboratories Final Report 43080. Acute Toxicity of ENA 713 to *Selenastrum capricornutum* Printz. 14. June 1996
- ABC Laboratories Final Report 43078. Static Acute Toxicity of ENA 713 to *Daphnia magna.* 13. June 1996
- RCC study no.: B40476. ENA713DS. Effect on Survival and Reproduction of *Daphnia magna* in a Semi-Static Test over Three Weeks. Final report: 13. May 2008
- ABC Laboratories, Final Report 43079. Static Acute Toxicity of ENA 713 to Bluegill (*Lepomis macrochirus*). 12. June 1996
- RCC study no.: B40498. ENA713DS. Toxic Effects to Zebra Fish (*Brachydanio rerio*) in an Early-Life Stage Toxicity Test. Final report: 23. April 2008
- RCC Study No.: B40465. ENA713 DS. Toxicity to Activated Sludge in a Respiration Inhibition Test. Final Report: 17 Dec 2007
- Harlan Laboratories Study No.: C06282. Effects of ENA713 DS on the Development of Sediment-Dwelling Larvae of *Chironomus riparius* in a Water-Sediment System. Final report: 19. May 2009.
- ABC Laboratories Final Report 42970. Aerobic Biodegradation of ENA 713 in Water. 07. March 1996
- RCC study number B40454.
- ABC Laboratories Final Report 42967. Determination of the Octanol/Water Partition Coefficient (Shake Flask Method) of ENA 713. 15. August 1996

- Novartis Core Data Sheet Exelon® (rivastigmine), Version 2.0, 27 May 2014.